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Estimating Excess Length of Stay due to Healthcare-Associated Infections: A Systematic Review and Meta-Analysis of Statistical Methodology.

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250 word structured summary

Background: Healthcare-associated infection (HAI) affects millions of patients worldwide. HAI is associated with increased healthcare costs, owing primarily to increased hospital length of stay (LOS) but calculating these costs is complicated due to time-dependent bias. Accurate estimation of excess LOS due to HAI is essential to ensure we invest in cost-effective infection prevention and control (IPC) measures.

Aim: To identify and review the main statistical methods that have been employed to estimate differential LOS between patients with, and without, HAI; to highlight and discuss potential biases of all statistical approaches.

Methods: A systematic review from 1997 to April 2017 was conducted in PUBMED, CINAHL, PROQUEST and ECONLIT databases. Studies were quality assessed using an adapted Newcastle-Ottawa Scale (NOS). Methods were categorised into time-fixed or time-varying with the former exhibiting time-dependent bias. We use two examples of meta-analysis to illustrate how estimates of excess LOS differ between different studies.

Findings: Ninety-two studies with estimates on excess LOS were identified. The majority of articles employed time-fixed methods (75%). Studies using time-varying methods are of higher quality according to NOS. Studies using time-fixed methods overestimate additional LOS attributable to HAI. Undertaking meta-analysis is challenging due to a variety of study designs and reporting styles. Study differences are further magnified by heterogeneous populations, case definitions, causative organisms and susceptibilities.

Conclusions: Methodologies have evolved over the last 20 years but there is still a significant body of evidence reliant upon time-fixed methods. Robust estimates are required to inform investment in cost-effective IPC interventions.

1 Introduction

Healthcare-Associated Infection (HAI) is a major issue for health providers, patients and public authorities worldwide.[1] The total annual number of patients with an HAI in European acute care hospitals was recently estimated at 3.2 million.[2] HAI has been associated with a significant impact on morbidity and mortality and can create substantial excess costs for health provision by prolonging hospital stay.[3] Accurate measurement of HAI costs is essential for developing cost-effective Infection Prevention and Control (IPC) measures. A major component of these costs can be captured by measuring the additional Length of Stay (LOS) due to HAI.[4, 5] This is complicated due to the fact that infection increases the duration of hospital stay but, at the same time, the risk of infection increases with duration of stay.[6] In addition, patients with longer LOS tend to be more at risk of HAI due to various characteristics and co-morbidities. HAI should be treated as a time-dependent event that is not present on admission otherwise estimates of excess LOS are biased.[3, 6-8]

A number of literature reviews have focused on LOS and economic burden due to HAI. Shulgen et al reviewed two studies to illustrate the concept of time-dependent bias. [9] Mitchell et al published an integrative review on statistical methods used to examine LOS due to *C. difficile* infections with a focus on time-dependent bias.[10] Gandra et al examined antimicrobial resistance and discuss time-dependent bias when estimating cost.[11] De Angelis et al made the case for focusing on LOS when estimating HAI economic burden, reviewed methods to estimate LOS and criticised time-fixed methods that treat HAI as artificially present on admission.[12] Seven studies were reviewed by Nelson et al who highlighted the issue of time-dependent bias by comparing methods that treat HAI exposure as time fixed versus a time varying event.[13] Fukuda et al reviewed analytical methodologies for estimating additional healthcare cost of HAI.[14] They raise the importance of adjusting for LOS and employing good statistical methods. Stone et al reviewed economic analyses of HAI and recommended use of guidelines and appropriate methods.[15] Variability in methods estimating the economic cost of HAI arises for a number of reasons; these include differences in case definitions, patient populations and whether the study design is prospective or retrospective.[11] It has been suggested that

meaningful comparisons can only be made if uniform definitions of rates are adopted along with standardised methods of data collection.[16] More recently Perencevich et al stated that stringent research standards are required to make the case for investing in IPC interventions, with a blueprint on how to achieve this.[17] It is uncertain whether these recommendations have been fully adopted. In the UK the main findings from the seminal Plowman study are still referenced but we should recognise the methodological limitations.[18]

In this paper we present a systematic review with two aims. First, to identify and review which statistical methods have been used to estimate differential LOS between patients with, and without, HAI and second, to assess the quality of studies and illustrate differences between the statistical methodologies with a particular focus on time-dependent bias. This is a unique review of studies with excess LOS estimates across all HAI types during the last twenty years. The review examines the current standard of research, identifies methods to estimate excess LOS due to HAI and proposes recommendations for the future.

2 Methods

This systematic review is PROSPERO registered (registration number: CRD42016050094); it adheres to recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and guidance from the Campbell and Cochrane Economics Methods Group on incorporating economic evidence into systematic reviews.[19, 20]

The literature was reviewed from 1st January 1997 to 30th April 2017 to identify relevant English language articles published in PUBMED, CINAHL, PROQUEST and ECONLIT databases. The search strategy combined the general “Cross Infection” MeSH heading with various nosocomial infection terms, major HAI types and economic or LOS terms (Appendix 1). HAI types were categorised based on European Centre for Disease Prevention and Control (ECDC) definitions.[21] Given the changing nature of acute hospital care, a 20 year period was chosen in order to include as many studies as possible while retaining studies that are still relevant today.

2.1 Selection criteria

All studies were assessed for eligibility by applying the PICOS (population, intervention, comparison, outcomes and setting) question format.[19] Publications identified in the search were combined and duplicates removed. A two-step review process was undertaken. The first step consisted of a title-abstract review and the second step of a full article review. Two authors (SM, SS) independently examined the titles and abstracts identified by the search strategy to select articles. Studies that were identified by only one author (SM) were discussed by a third (AM) to determine if they met the eligibility criteria for inclusion in the Review. Disagreements were resolved by discussion between the three authors (SM, SS, AM).

The PICOS inclusion and exclusion criteria applied were:

- **Population** We included studies with adult inpatients that had a documented HAI in a health facility. Studies were excluded if they did not clearly distinguish between colonisation, community onset infections or HAI. Studies without a non-HAI comparison group were excluded.

- **Intervention** We included observational studies; interventions were not considered when including or excluding papers.

- **Control/design** We included case controlled and cohort studies. Case controlled studies allocated patients according to their HAI status. Commentaries and reviews were excluded.

- **Outcome** Studies were included if they attempted to measure and report LOS using any statistical method. Studies which did not report LOS data were excluded. Studies were required to report total LOS from admission to discharge. Studies measuring partial LOS were excluded (e.g. only reporting duration of stay in a single specialty).

- **Setting** We included studies in any health care setting with populations typical of acute care inpatient wards and critical care units. We excluded studies with selected populations; inpatients and outpatients or patients in residential care.

2.2 Data extraction

An initial scoping review was undertaken for the selected papers with a set of classifications developed for analysis types. Six statistical methods were identified and divided into two high level groups. The first group treats HAI as present on admission or as time fixed and the second treats HAI as a time-dependent event or as time varying. Studies that did not match on the timing of infection will be referred to as Matching (Simple) and studies that matched on the timing to infection are referred to as Matching (Time). Group comparison, Matching (Simple) and regression techniques that do not take the timing of events into account are referred to as time-fixed. Matching (Time), Survival Analysis and Multistate Modelling control for the time-dependence of HAI are referred to as time-varying.[13] Survival analysis can also be a time-fixed approach but the identified survival analysis studies treated HAI as time-varying and therefore survival analysis was placed in the second group. A more detailed description of these methodologies is described within Supplementary material 5.

Extraction of data was performed by one investigator (SM). Two authors (SS, AM) checked 10% of this work for consistency. Any disagreements were resolved by consensus of these three authors. Data extraction was recorded on a Microsoft Excel template with the following columns: authors, year of publication, HAI type, organism (if reported), study design, statistical method, excess LOS due to HAI, confidence interval, sample size, year of data collection, journal title, country, country income classification, hospital setting, information on antibiotics (Yes/No) and discussion of time-dependent bias (Yes/No). Countries were grouped into high and middle income based on the World Bank country income classification.[22]

HAI type was defined based on the way papers reported their results. When papers reported outcomes for different HAI types we extracted these separately. We defined an HAI group where papers reported results for multiple types of HAI in a single measure. For example, a paper that reported the cost of HAI overall without distinguishing between the different subtypes would go into this group. Excess LOS due to HAI was not always available as a separate estimate since some studies reported LOS outcomes separately for an HAI and a non-HAI group. There were notable differences in the way studies reported their

estimates and therefore we only report LOS outcomes in the studies selected for meta-analysis. Most studies reported standard deviations or confidence intervals but only standard errors or p-values were provided in some papers. Studies using regression methods or multistate modelling reported estimates of impact on LOS in excess days with a 95% confidence interval. When more than one method was used we extracted the main method and associated estimate. For example, when group comparison estimates were present along with estimates from another method we only extracted the latter. For bloodstream infection studies, we extracted multiple estimates for a single HAI (see section 2.4). We followed recommendations by the Cochrane collaboration for calculating confidence intervals in studies where this information was not provided.[19]

2.3 Quality Assessment

Quality assessment was carried out using Newcastle Ottawa Scale (NOS).[23, 24] NOS is a quality assessment tool for use on nonrandomized studies included in systematic reviews, specifically cohort and case-control studies. A star rating system is used to indicate the quality of a study, with a maximum assessment of nine stars.[24] Each criterion receives zero, one or two stars with more stars indicating higher compliance. As suggested by the Cochrane collaboration we modified NOS to represent issues specific to studies estimating excess LOS due to HAI.[19] Our version of NOS assesses study design, HAI case definitions and application of appropriate statistical methods. The main changes from the original NOS are defining the exposure as HAI, the outcome as LOS, wording to reflect application of case definitions and allocation of one star to studies employing a time-varying statistical method. The rest of the criteria are the same as the original NOS. The only items where it was possible to receive two stars was for applying internationally recognised case definitions to records, e.g. CDC and ECDC, and for employing appropriate sampling strategies either as cohort or case control studies. The maximum number of stars possible was eight. One author (SM) assessed all included articles and two authors (SS, AM) checked 10% of this work for consistency. Any disagreements were resolved by consensus of the three authors. Supplementary material 3 details the version of NOS applied to the articles included in this review. Quality assessment was done for each LOS estimate separately. Table I shows the

total number of stars awarded to each LOS estimate and Supplementary material 4 provides a detailed breakdown of quality assessment.

2.4 Statistical Analysis

Stata statistical software was used to conduct all statistical analyses.[25] A Wilcoxon-Mann-Whitney (WMW) test on the equality of means was performed to test if statistical methodology has an impact on article quality. When applying this test we excluded the NOS item on statistical methods since only time-varying methods could be allocated a star there. Meta-analysis: As discussed earlier the study designs showed a large amount of heterogeneity. In order to minimise differences in populations and potential impact on excess LOS, we focused on high income countries and chose two commonly occurring HAI types. The first meta-analysis focuses on estimates of impact of Bloodstream Infection (BSI) (17 studies) on LOS and the second on Gastrointestinal Infection (GI) (19 studies) caused by *Clostridium difficile* (CDI). Bloodstream infections are known to increase LOS and cause significant impact on patient morbidity and mortality.[26] HAI CDI was selected as it is a single causative organism associated with diarrheal disease and would provide an important difference on statistical methodology in the CDI meta-analysis. CDI HAI obviates the variation due to different causative organisms present in the BSI infections. The heterogeneity among studies was estimated by the I^2 statistic.[27] We used a random-effects estimator to calculate pooled estimates of excess LOS due to HAI.[27, 28] The Stata metan routine was used to display meta-analysis results graphically in forest plots.[25, 29] For meta-analysis we extracted excess LOS estimates in days and calculated standard errors as recommended by the Cochrane collaboration. In cases where LOS of cases and controls was available separately, we extracted LOS for both of these groups and calculated the difference. Where different estimates for susceptible and resistant organisms were reported we extracted excess LOS for both. In the BSI group we extracted 31 excess LOS estimates from 17 studies where more than one method was used or information on more than one organism or different antibiotic susceptibilities were reported. In the CDI group we extracted one estimate from each study, 19 estimates in total.

3 Results

The main characteristics of the studies included and the statistical methods identified are shown on Table I. There were: 23 studies[26, 30-51] with an estimate of impact of BSI on LOS; 22 studies[50, 52-72] with estimates from the impact of GI; 27 studies[37, 42, 43, 47, 50, 73-94] with estimates from surgical site infection (SSI); 26 studies[4, 43, 47, 50, 79, 80, 85, 95-113] with an average estimate from all types of HAI; ten studies[35, 37, 42, 43, 45, 47, 50, 80, 114, 115] with estimates from urinary tract infection (UTI); eight studies[35, 37, 42, 47, 114, 116-118] with estimates from pneumonia; four studies[43, 50, 80, 99] with estimates from lower respiratory tract infection (other than pneumonia); and one study[119] of bone and joint infection. In total we extracted 121 LOS estimates shown in supplementary material 1 from 92 studies.

See supplementary material 1 for a summary of the characteristics of the published studies. Some authors reported more than one infection type and therefore appear in multiple HAI groups. Studies employed data collected in multiple years and there was some overlap between selected studies. Table I shows the types of infections, statistical methodologies used to estimate excess LOS, country study design and year. As described earlier statistical methods were categorised in time-fixed and time-varying according to their treatment of the timing of HAI.[13]

There were 81 studies[4, 26, 31-39, 41-43, 46-71, 73-77, 79-95, 97, 99-102, 104-107, 109-117, 119] from high income countries, of which 40% took place in the US and 22% in the UK, Spain and Australia, and eleven studies[30, 40, 44, 45, 72, 78, 96, 98, 103, 108, 118] from middle income countries. The majority (80%) of studies were cohort studies and we included 18 studies with a case-control design. The case-control design applies to the sampling strategy where one or more controls were chosen for each HAI case. These type of studies are also known as case-control with follow up[120]. The majority of the studies collected data during the period 2005 to 2012. The most frequent statistical method employed in the included articles is simple matching (31 studies, 34%) followed by regression (24 studies, 26%), group comparison (14 studies, 15%), matching on time (12 studies, 13%), multistate modelling (9 studies, 10% and survival analysis (2 studies, 2%). There were 12 studies that investigated more than one HAI types and from these we

extracted more than one estimates, one for each HAI.[35, 37, 42, 43, 45, 47, 50, 79, 80, 85, 99, 114]

Figure 2 shows trends in statistical techniques in published articles over the last two decades. Time-fixed methods are the largest proportion (73%) of statistical techniques used to estimate excess LOS. In our sample studies using time-varying methods appear in 2006 and 59% of these used matching on time to infection techniques.[85] Group comparison studies are still being published and 12% of articles have used this method since 2006. Overall, only 32% of studies published since 2006 have used time-varying methods.

Figure 3 shows that time-fixed methods have been used in the majority of articles in every year except 2008. Time-fixed methods continue to be the most common methodology used in HAI studies. This review included two survival analysis studies and nine multistate modelling studies (Table I). Nine articles from middle income countries used either a group comparison [72, 96, 98, 108, 118] approach or a simple matching method.[40, 44, 78, 103] One article from the middle income country group used a regression model[45] and one article used matching on the time to infection.[30]

Quality assessment NOS scores of seven or eight were considered as high-quality, five or six as moderate quality and low quality for less than five. Approximately 57% of estimates were of high quality receiving seven or eight stars. Articles using time-varying methods are of higher quality than articles with time-fixed methods. Figure 4 summarises the results of the quality assessment by type of statistical method. NOS allocates seven stars out of eight to study design. Articles using time-varying methods scored significantly (z=3.172, P<.002) higher in the quality assessment. When performing the WMW test we excluded the NOS item that is related to methods since only time-varying methodologies could be awarded a star and we wanted to compare quality as captured by the NOS items on study design. One reason that time-fixed methods were assessed to be of lower quality is that only 55% of these applied case definitions to identify cases. 23% of the time-fixed studies scored zero stars in the relevant NOS item as they used retrospective case ascertainment using (International Classification of Disease) ICD codes or treatment.[121]

3.1 Meta-analyses

For the BSI meta-analysis two studies reported results for more than one organism.[26, 32] Five studies reported results for susceptible and resistant organisms separately.[26, 33, 36, 46, 49] Three studies reported results using more than one statistical method.[33, 47, 51] Time-fixed methods consistently produce higher estimates of HAI impact on LOS with larger confidence intervals. In the BSI meta-analysis the focus is on within-study differences and we found that the causative organism and susceptibility have a big impact on excess LOS due to HAI; these should always be taken into account when calculating the economic impact of BSI in different settings.

Figure 5 presents the results of the meta-analysis in the BSI articles grouped by statistical method. There is considerable variability in the estimates with a range of 1.2 to 26.4 excess days due to HAI. Among studies that used more than one statistical method two studies show that estimated excess LOS can increase substantially if patient characteristics and comorbidities are ignored by using group comparison as opposed to regression or simple matching.[33, 47] Vrijens et al show that ignoring BSI as a time-dependent event by using time-fixed methods more than doubles the estimated excess LOS.[51] Heterogeneity is very high in every group with the matching on time group having the lowest I^2 of 82%. One reason for the high heterogeneity is that these studies examine a range of organisms associated with BSI. Studies that did not estimate impact of specific organism but had access to laboratory results reported that *S. aureus* was one of the most common causes of BSI in their samples.[32, 39, 46, 51] Stewardson et al estimate the impact of susceptible and resistant Enterobacteriaceae and *S. aureus* BSI using multistate modelling and find that the estimated impact of the susceptible BSI infections on LOS approximately doubles when *S. aureus* is the causative agent.[26] The study by Barnett et al shows that BSI caused by Gram positive bacteria have a much greater impact on LOS than BSI caused by Gram negative bacteria.[32] Figure 5 shows that antimicrobial resistance (AMR) increases estimated LOS and there are noticeable differences between causative pathogens.[26, 32, 33, 49] The variability in the BSI studies contrasts to the second meta-analysis focusing on a single organism to isolate the impact of statistical method on the estimates.

We extracted 19 estimates from 19 studies estimating excess LOS due to Healthcare Associated (HA) CDI in high income countries (Figure 6).[52-63, 65-71] The HA CDI studies focus on a single infection type caused by the same organism and estimates in each statistical group were homogenous as shown by the low I^2 scores within each analysis group in Figure 6. The overall I^2, which can be calculated by analysing studies as a single group, was very high (99.7%) and resembled I^2 scores in the BSI studies. Figure 6 shows that the results should be analysed separately for each statistical methodology. The CDI results display a large variability in LOS estimates on the impact of CDI with a range of 1 to 16 excess days. Since CDI is a commonly occurring HAI even a small number of extra days can have a significant impact on cost estimates due to CDI.[122] Time-fixed methods produce consistently higher estimates of excess LOS due to CDI. This finding is particularly evident in studies using regression methods and simple matching studies, which show higher heterogeneity and much higher and uncertain estimates of LOS when compared to time-varying methods. The impact of BSI and CDI on LOS is consistently overestimated when time-fixed methods are used.

4 Discussion

This systematic review found that there are six main statistical techniques which have been used over the last 20 years to assess excess LOS due to HAI. These methods can be grouped in time-fixed and time-varying according to their treatment of time-dependence. We found a significant body of evidence that does not take into account the time-dependent nature of HAI due to the use of time-fixed methods. Even though time-varying methods appeared more than ten years ago the majority of articles in high income countries still use time-fixed methods to estimate excess LOS due to HAI. In middle income countries (where sophisticated data are not routinely collected due to funding constraints) we only identified one study that controls for time-dependence.[30]

The ability to synthesise evidence from multiple studies is key if policymakers and researchers are willing to model the cost-effectiveness of IPC interventions. Despite a large number of publications on each type of infection it is challenging and sometimes inappropriate to synthesise evidence due to the fact researchers use different study designs, statistical methods and reporting styles. There are inherent difficulties in HAI literature due

to the range of different infection types, settings, patient types, organisms and AMR. However, we found that papers often magnify these differences by using time-fixed methods. This limits our ability to synthesise evidence, even in cases where studies investigate a single HAI type or a single organism. When looking at a single infection (BSI) the meta-analysis has shown that causative organisms and antibiotic resistance have a large impact on the excess LOS estimates. Where synthesising evidence appeared possible (CDI) meta-analysis showed that the choice of statistical method can have a highly distortive effect on excess LOS estimates. The meta-analysis of the BSI studies suggests that defining a high level infection type (such as BSI) is not sufficient to perform synthesis when trying to estimate economic impact since this can hide substantial heterogeneity between studies. So other than choosing studies that account for time-dependence bias it is also important to be clear about organism identity, patient conditions and AMR in the studies of the meta-analysis. The meta-analysis of CDI studies confirmed previous work which suggests time-fixed methods overestimate the burden of HAI when compared to time-varying.[113] We suggest that researchers take into account all the above when performing meta-analysis to estimate economic cost of HAI.

IPC planning at international, national or local levels requires accurate cost estimates and therefore excess LOS precision. IPC measures aim to prevent HAI cases in order to improve clinical effectiveness and maximise health benefits.[13] Identifying which combination of HAI and patient characteristics causes the greatest economic burden should help focus investment in interventions that give the greatest return. The main cost attributable to HAI is the additional stay in the hospital.[5, 7, 77, 123] Preventing HAI can lead to released bed days, reduction in waiting times and the ability to treat more patients. Modelling studies that synthesise evidence from different sources can inform policy related to IPC measures.[124] Nevertheless, it is of the utmost importance that modelling studies are based on well-designed studies otherwise recommendations on cost-effectiveness of IPC interventions become unreliable.

Our results agree with previous work, which suggests that estimates from time-varying methods that control for time-dependent bias should be adopted when making policy decisions.[7, 12, 13] Time-fixed methods suffer from time-dependent bias and studies employing such methods are of lower quality overall. Each study is conducted in inherently

different circumstances with differences in characteristics of the study population and methodologies. There are also differences in the way LOS outcomes are reported complicating the process of synthesising results. Some studies were excluded from this review because it was not clear if cases were healthcare associated infection, colonisation, community acquired infection or a combination. Since IPC interventions are designed to target HAI and not community onset infection, only studies that clearly show that outcomes are HAI-specific should be used for planning policy.

There is already an acknowledged requirement for structured reporting of observational studies with the STROBE statement and economic evaluation studies with the CHEERS statement. Studies investigating HAI burden are observational studies which fall within the scope of STROBE.[125, 126] Analytical methodologies have evolved and reporting guidelines have not accounted for all these developments and should also be updated. Studies that fully meet the STROBE recommendations will not necessarily avoid time-dependent bias or measurement bias in their results. Our recommendation is that additional aspects of study design and reporting should be considered especially within studies reporting HAI and antimicrobial resistance.

Overall recommendations are:

1) Studies can have either a cohort or a case-control design but always ensure that the comparator group is clearly defined especially when reporting AMR outcomes.
2) Studies should employ appropriate case definitions, ideally internationally recognised definitions applied to records and clearly distinguish between HAI and community-onset or colonisation.
3) Studies should collect data on the timing of events and control for time-dependent bias by using a time varying analytical methodology
4) Studies should report results from a multi-state model or if these are not available patient-days of HAI and non-HAI patients.
5) Studies must clearly state if LOS was measured from admission to discharge or if LOS was partially measured e.g. LOS within ICU.

This review indicates that excess LOS estimates based on statistical methods that treat HAI as a time-varying exposure show a shorter estimated extra stay. This means that HAI costs may have been overestimated.[5, 6, 10, 13, 68, 113, 127] Time-dependent bias and different

statistical methods lead to highly variable estimates, which might lead to inefficient policies. Beyersmann et al show that time-dependant bias is large in methods such as regression methods and survival analysis that do not normally treat HAI as a time-varying exposure.[128] Common regression methods cannot control for the timing of events and caution should be exercised when applying or interpreting regression results.[129] Regression methods to estimate excess LOS should only be used for associations rather than causal inference.[41] Survival analysis is normally a time-fixed method but it can be adapted; the two survival analysis studies included in this review treat HAI as time-varying.[58, 85]

Matching methods should match on time to infection requiring the control patient to have spent an equivalent time in hospital before the infection as the case.[36, 51] This will not completely eliminate time-dependent bias but it will significantly reduce it. Nelson et al compare three estimation strategies and show that matching on the time to infection can substantially reduce time-dependence bias.[113] Matching on time to infection should be ideally performed by using incidence density sampling. This produces similar estimates to multistate modelling although with less precision and wider confidence intervals.[3] A combination of these two methods was used by Barnett et al who applied multistate modelling to a sample that was matched using incidence density sampling.[32] The recommended approach to estimate excess LOS is multistate modelling.[4] Wolkewitz et al (2017) show that if information on event counts or patient days is available it is possible to perform basic multistate analysis.[130] However, a limitation of multistate models in the past was that they were not able to control for patient characteristics. Stewardson et al demonstrate an approach to indirectly control for age and comorbidities using a multilevel model.[26] In most cases HAI patients have greater severity of illness and comorbidities when compared with non-HAI patients. Since severity of illness and comorbidities are also predictors of LOS it is important to control for these because such variables may distort the relationship between infection and LOS.[17]

One reason for the lack of studies that control for time-dependent bias may be the data requirements for these methods, e.g. knowing the day the infection began during a patient's hospital stay. Only if this information is available can researchers employ statistical methods that control for time-dependent bias. We identified US studies that frequently use the

National Inpatient Sample (NIS).[31, 35, 56, 57, 65, 71, 115, 119] These studies use ICD codes to identify cases but NIS data do not provide information on the timing of infection forcing researchers to use time-fixed methods to estimate impact of HAI on LOS. These studies received the lowest scores in the quality assessment and estimates should be treated with caution. Barnett et al published a detailed description of how time-dependent data can be organised for use in statistical models.[129] An estimate of only a few days excess stay in hospital can have a large impact on total cost. For example, the cost of an excess bed-day in 2015-2016 has been estimated at £306 and there were 1,398 CDI cases in 2016 in Scotland.[131, 132] Every extra day of estimated excess LOS due to CDI would appear to cost an additional £427,788 to the Scottish NHS. We recognise that for this calculation we have not used unit costs that reflect the opportunity cost of the bed-day and these would be expected to be lower than £306.[133] Even though the exact figure can be challenged on the basis of not being a pure opportunity cost we have seen that time-fixed methods can overestimate this effect for CDI by up to seven times. Irrespective of using accounting or opportunity costs excess LOS should be estimated using time-varying methods.

We propose that methods that minimise time-dependent bias are used to inform models of cost-effectiveness because only after establishing estimates through appropriate research methods can we combine findings from multiple studies to inform policy decisions. Following the recommendations of this review would improve our ability to undertake both meta-analysis and modelling studies. This will help to develop more precise estimates of the effects of interventions by ensuring use of studies with as low bias as possible especially measurement and time-dependent bias. In general, more and better designed studies are needed in order to provide accurate data to support effective and efficient IPC interventions.[14]

5 Conclusions

Accurate quantification of additional costs of HAI is essential for developing cost-effective IPC measures. A range of statistical analyses have been used to address the question of excess LOS as a result of HAI. Availability of specific data item and study design can dictate

researchers' ability to employ time-varying statistical techniques. As with all research that requires data collection there is a balance to be struck in terms of resource intensive data collection and requirements for analysis. When measuring economic impact, a major component of HAI costs can be captured by measuring the additional LOS due to these infections. We recommend that studies collect accurate information on the timing of key events such as time of admission, time of infection and time of discharge. Combining this information with patient characteristics and co-morbidities with appropriate statistical methods such as survival analysis; multistate modelling; or matching on time to infection minimises bias when estimating impact on LOS. Better study design, analytical techniques and reporting are needed to improve the quality of evidence worldwide. Further research is needed to identify the impact of HAI, including in middle and low income countries where data availability is limited due to funding constraints.[134]

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Tables

Table I: Summary of characteristics of published studies that produced estimates of excess LOS due to HAI. Where studies reported more than one HAI type we extracted all LOS estimates.

Study Characteristics		
HAI type(s) Reported:	No of studies	(%) of studies
Bloodstream	23	(19%)
Gastro-intestinal	22	(18%)
Surgical site	27	(22%)
HAI*	26	(22%)
Urinary tract	10	(8%)
Pneumonia	8	(7%)
Lower respiratory tract	4	(3%)
Bone and joint	1	(1%)
Primary Statistical Methodology:		
Time-Fixed		
Group Comparison	14	(15%)
Matching (Simple)	31	(34%)
Regression	24	(26%)
Time-varying		
Matching (Time)	12	(13%)
Survival Analysis	2	(2%)
Multistate Model	9	(10%)
Total	92	(100%)
Included Studies by Country and Income Classification:		
High Income	81	(88%)
Middle Income	11	(12%)
Study Design		
Case-Control	18	(20%)
Cohort	74	(80%)
Studies' Year of Data Collection**		
1989-2000	38	
2001-2004	37	
2005-2008	54	
2009-2012	43	
2013-2016	10	

* HAI refers to studies which estimated total impact on LOS across more than one type of HAI or multiple types of HAI due to a single organism (e.g. MRSA).

**Counted if contain any data collected in these years (most studies used data collected in multiple years)

Figures

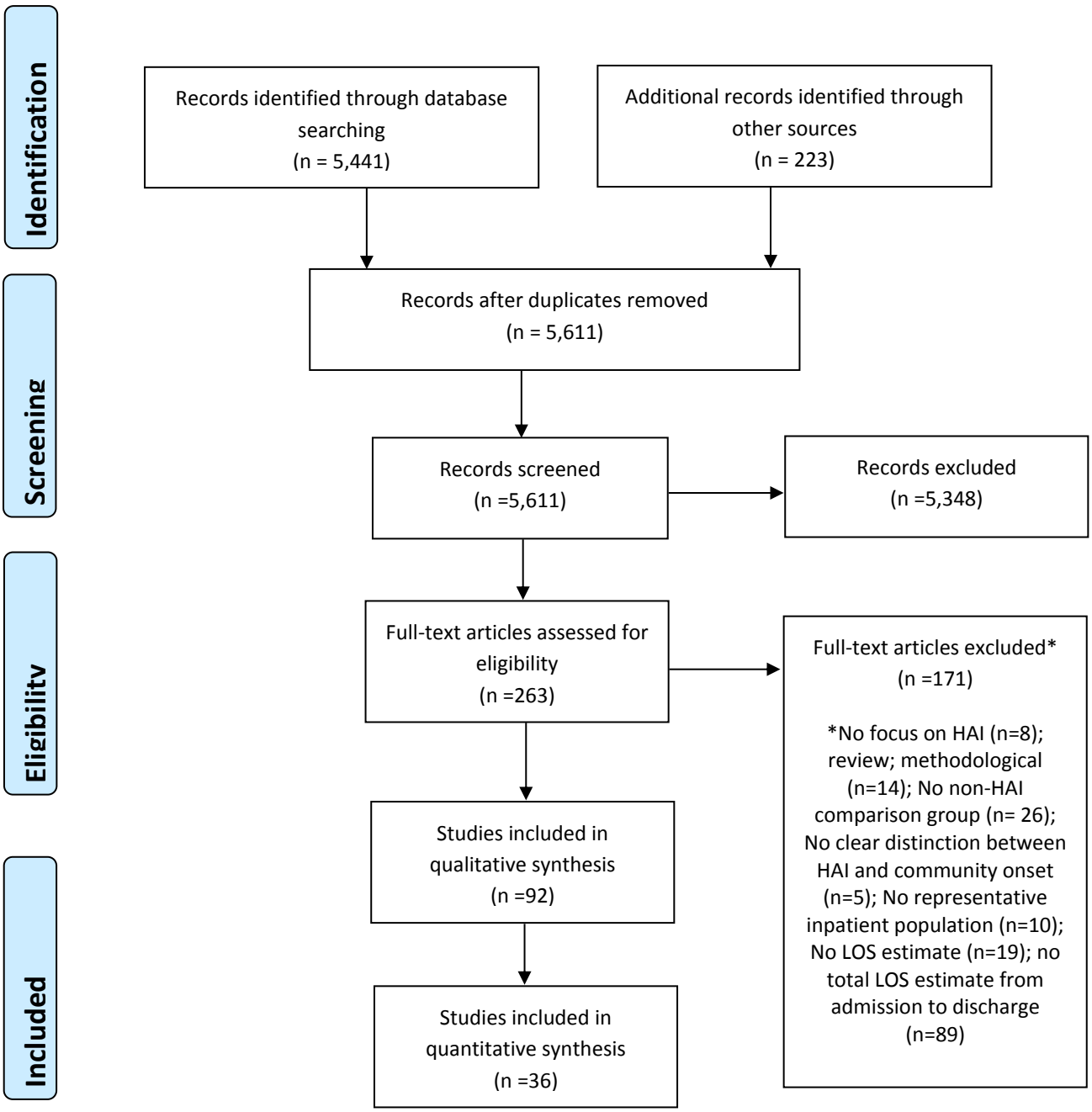

Figure 1: PRISMA Flow Diagram showing the relevant observational studies of the impact of HAI on LOS

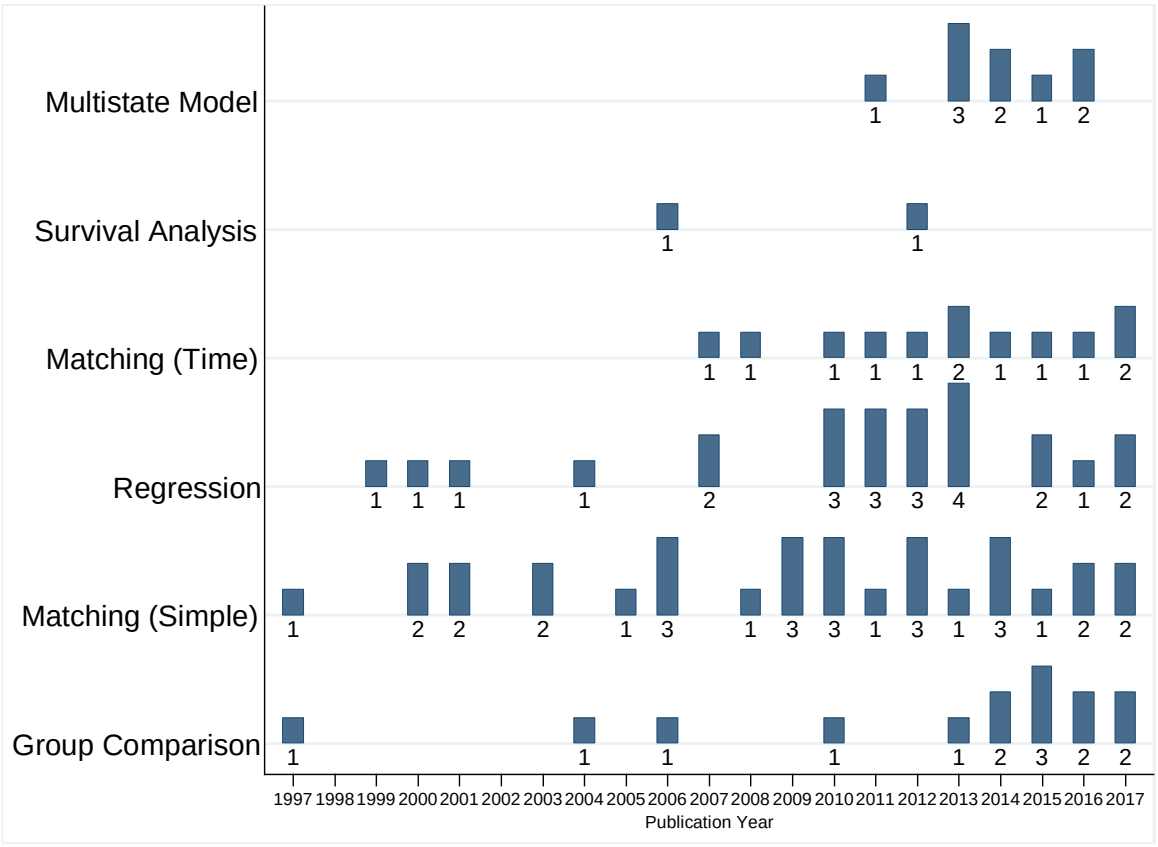

Figure 2: Articles by year of publication and statistical method. Number of studies published in the corresponding year are shown below each bar. Group comparison, Matching (Simple) and Regression are time-fixed methods. Matching (Time), Survival Analysis and Multistate Modelling are time-varying methods.

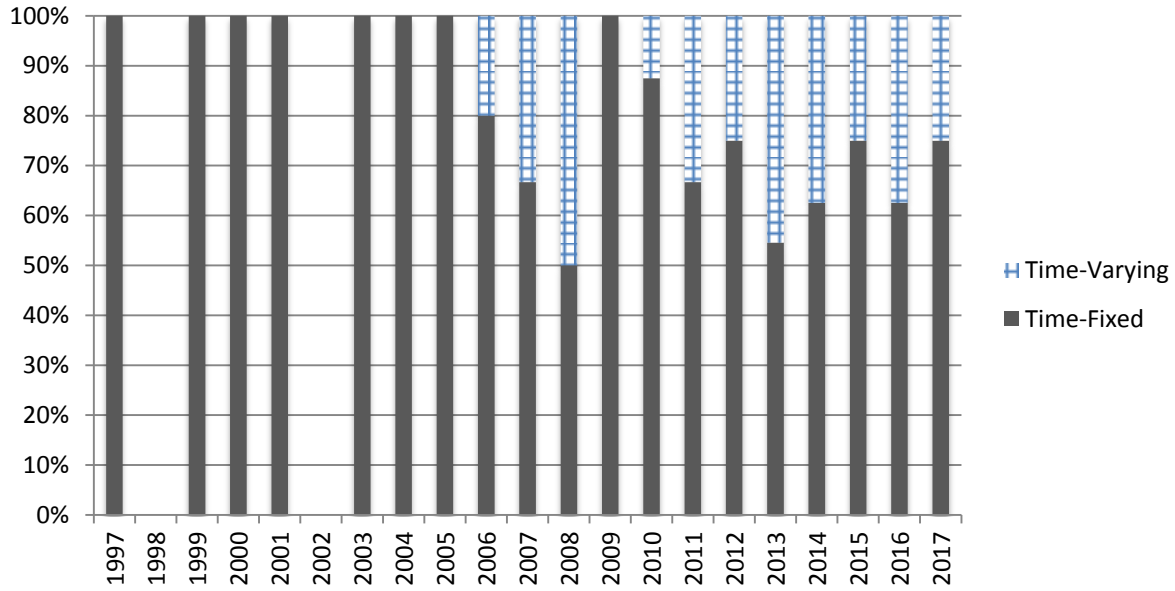

Figure 3 Articles by year of publication and time-fixed vs time-varying methodologies.

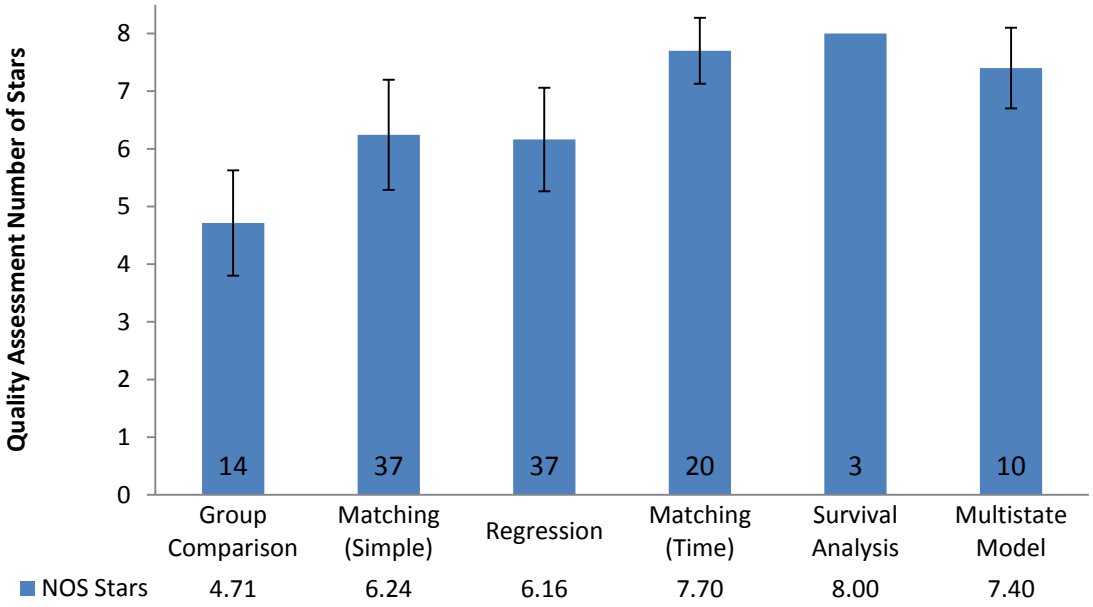

Figure 4: Quality assessment by type of statistical method. Papers quality assessed using the NOS assessment tool for case-control and cohort studies. Studies could get a maximum of 8 stars. 121 LOS estimates quality assessed in 92 studies. Number of estimates assessed in each statistical method are shown on the bottom of each bar. Mean NOS stars by method are shown below each bar. There were three LOS estimates in the Survival Analysis group which were allocated a perfect score of 8 stars. Error bars calculated from standard deviations. Group comparison, Matching (Simple) and Regression are time-fixed methods. Matching (Time), Survival Analysis and Multistate Modelling are time-varying methods.

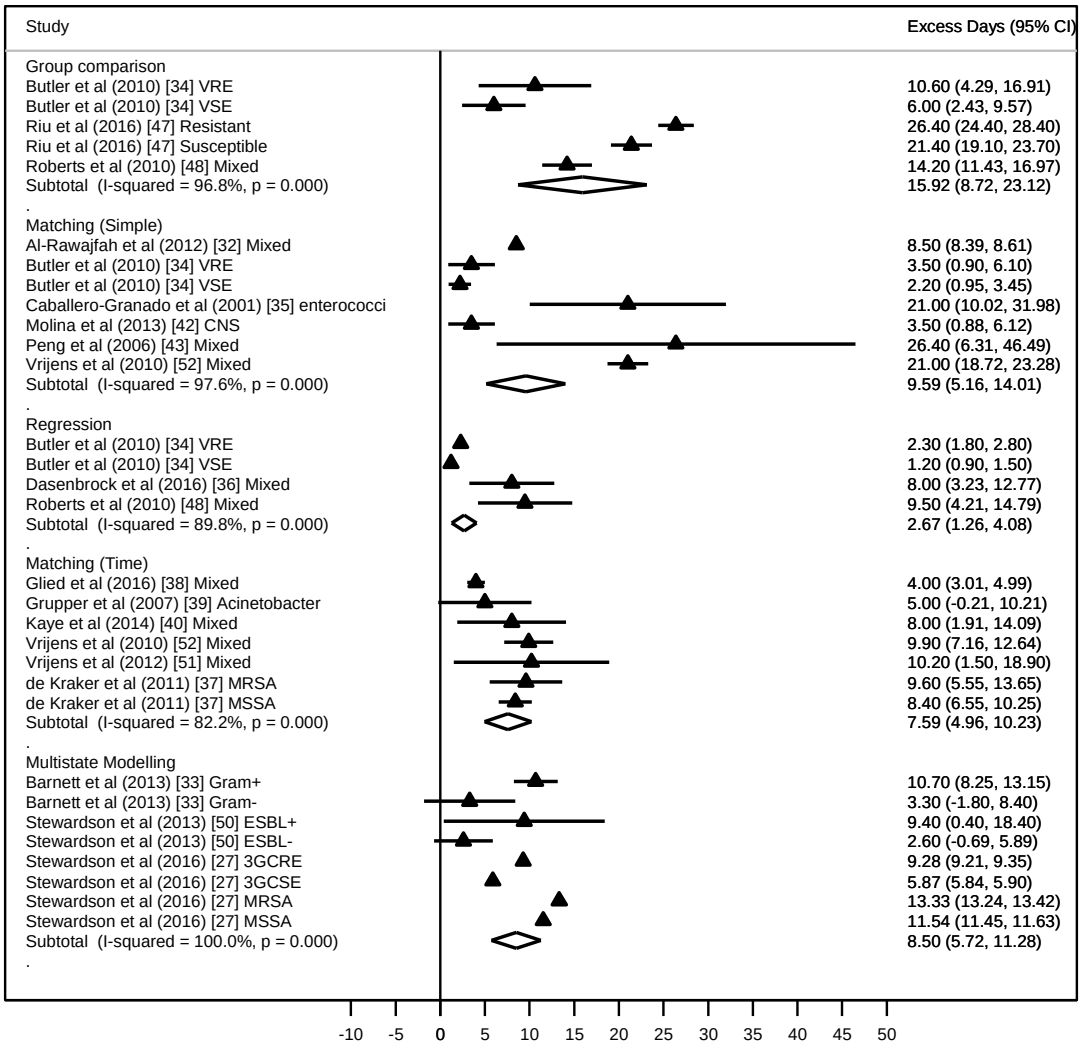

Figure 5: Excess days and 95% CIs for the association of LOS and BSI. The triangles and horizontal lines correspond to the study-specific Excess Days estimates and 95% CIs. The diamonds represent the pooled Excess Days and 95% CIs of each subgroup. The vertical solid line shows Excess Days of zero. Mixed: Range of organisms included, not separated by antimicrobial resistance. VRE: Vancomycin-resistant enterococci. VSE: Vancomycin-susceptible enterococci. CNS: Coagulase-negative staphylococci. MRSA: Methicillin-resistant *Staphylococcus aureus*. MSSA: Methicillin-susceptible *Staphylococcus aureus*. Gram+: Gram-positive bacteria. Gram-: Gram-negative bacteria. ESBL+: Extended-Spectrum β-Lactamase–Producing Enterobacteriaceae positive. ESBL-: Extended-Spectrum β-Lactamase–Producing Enterobacteriaceae negative. 3GCRE: Third-generation cephalosporin resistant Enterobacteriaceae. 3GCSE: Third-generation cephalosporin susceptible Enterobacteriaceae. Enterococci: Susceptible and resistant enterococcal BSI. Acinetobacter: Susceptible and resistant Acinetobacter BSI. Group comparison, Matching (Simple) and Regression are time-fixed methods. Matching (Time), Survival Analysis and Multistate Modelling are time-varying methods.

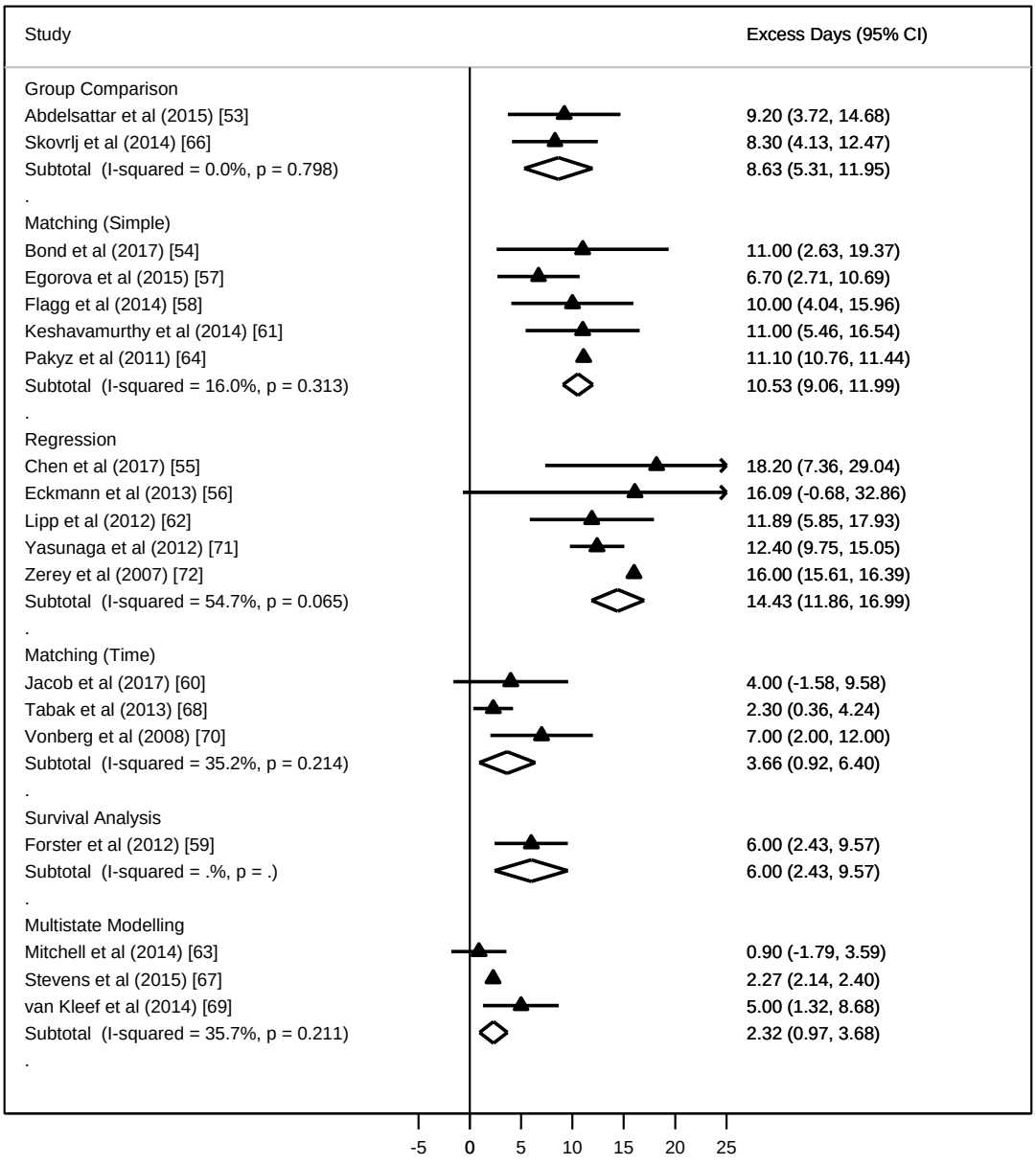

Figure 6: Excess days and 95% CIs for the association of LOS and CDI. The triangles and horizontal lines correspond to the study-specific Excess Days estimates and 95% CIs. The diamonds represent the pooled Excess Days and 95% CIs of each subgroup and overall population. The vertical solid line shows Excess Days of zero. Group comparison, Matching (Simple) and Regression are time-fixed methods. Matching (Time), Survival Analysis and Multistate Modelling are time-varying methods.

Figure Legends

Figure 7: PRISMA Flow Diagram showing the relevant observational studies of the impact of HAI on LOS

Figure 8: Articles by year of publication and statistical method. Number of studies published in the corresponding year are shown below each bar. Group comparison, Matching (Simple) and Regression are time-fixed methods. Matching (Time), Survival Analysis and Multistate Modelling are time-varying methods.

Figure 9 Articles by year of publication and time-fixed vs time-varying methodologies.

Figure 10: Quality assessment by type of statistical method. Papers quality assessed using the NOS assessment tool for case-control and cohort studies. Studies could get a maximum of 8 stars. 121 LOS estimates quality assessed in 92 studies. Number of estimates assessed in each statistical method are shown on the bottom of each bar. Mean NOS stars by method are shown below each bar. There were three LOS estimates in the Survival Analysis group which were allocated a perfect score of 8 stars. Error bars calculated from standard deviations. Group comparison, Matching (Simple) and Regression are time-fixed methods. Matching (Time), Survival Analysis and Multistate Modelling are time-varying methods.

Figure 11: Excess days and 95% CIs for the association of LOS and BSI. The triangles and horizontal lines correspond to the study-specific Excess Days estimates and 95% CIs. The diamonds represent the pooled Excess Days and 95% CIs of each subgroup. The vertical solid line shows Excess Days of zero. Mixed: Range of organisms included, not separated by antimicrobial resistance. VRE: Vancomycin-resistant enterococci. VSE: Vancomycin-susceptible enterococci. CNS: Coagulase-negative staphylococci. MRSA: Methicillin-resistant *Staphylococcus aureus*. MSSA: Methicillin-susceptible *Staphylococcus aureus*. Gram+: Gram-positive bacteria. Gram-: Gram-negative bacteria. ESBL+: Extended-Spectrum β-Lactamase–Producing Enterobacteriaceae positive. ESBL-: Extended-Spectrum β-Lactamase–Producing Enterobacteriaceae negative. 3GCRE: Third-generation cephalosporin resistant Enterobacteriaceae. 3GCSE: Third-generation cephalosporin susceptible Enterobacteriaceae. Enterococci: Susceptible and resistant enterococcal BSI. Acinetobacter: Susceptible and resistant Acinetobacter BSI. Group comparison, Matching (Simple) and Regression are time-fixed methods. Matching (Time), Survival Analysis and Multistate Modelling are time-varying methods.

Figure 12: Excess days and 95% CIs for the association of LOS and CDI. The triangles and horizontal lines correspond to the study-specific Excess Days estimates and 95% CIs. The diamonds represent the pooled Excess Days and 95% CIs of each subgroup and overall population. The vertical solid line shows Excess Days of zero. Group comparison, Matching (Simple) and Regression are time-fixed methods. Matching (Time), Survival Analysis and Multistate Modelling are time-varying methods.

Supplementary Material 1

Studies eligible for data extraction and analysis by HAI type. Note that some studies appear in more than one HAI type.

Authors	Study Design	Primary Statistical Methodology	Country	QA Stars
Bloodstream Infection				
Riu et al (2016)[46]	Retrospective cohort	Group comparison	Spain	6
Al-Rawajfah et al (2012)[31]	Retrospective case-control	Matching (Simple)	USA	4
Caballero-Granado et al (2001)[34]	Prospective case-control	Matching (Simple)	Spain	6
Kothari et al (2009)[40]	Retrospective case-control	Matching (Simple)	India	7
Molina et al (2013)[41]	Prospective case-control	Matching (Simple)	Spain	7
Peng et al (2006)[42]	Retrospective cohort	Matching (Simple)	USA	7
Primo et al (2012)[44]	Retrospective case-control	Matching (Simple)	Brazil	5
Song et al (2003)[48]	Retrospective cohort	Matching (Simple)	USA	6
Butler et al (2010)[33]	Retrospective cohort	Regression	USA	6
Dasenbrock et al (2016)[35]	Retrospective cohort	Regression	USA	5
Plowman et al (2001)[43]	Prospective cohort	Regression	UK	6
Rattanaumpawan et al (2017)[45]	Retrospective cohort	Regression	Thailand	7
Roberts et al (2010)[47]	Retrospective cohort	Regression	USA	7
Al-Rawajfah et al (2013)[30]	Retrospective case-control	Matching (Time)	Jordan	7
de Kraker et al (2011)[36]	Prospective cohort	Matching (Time)	Europe	7
Glied et al (2016)[37]	Retrospective cohort	Matching (Time)	USA	8
Grupper et al (2007)[38]	Retrospective cohort	Matching (Time)	Israel	6
Kaye et al (2014)[39]	Retrospective cohort	Matching (Time)	USA	8
Vrijens et al (2010)[51]	Retrospective cohort	Matching (Time)	Belgium	8
Vrijens et al (2012)[50]	Retrospective cohort	Matching (Time)	Belgium	8
Barnett et al (2013)[32]	Retrospective case-control	Multistate Modelling	Australia	7
Stewardson et al (2013)[49]	Retrospective cohort	Multistate Modelling	Switzerland	8
Stewardson et al (2016)[26]	Retrospective cohort	Multistate Modelling	Europe	7
Gastrointestinal Infection				
Abdelsattar et al (2015)[52]	Prospective cohort	Group comparison	USA	5
Skovrlj et al (2014)[65]	Retrospective cohort	Group comparison	USA	3
Zhang et al (2016)[72]	Prospective cohort	Group comparison	China	5
Bond et al (2017)[53]	Prospective case-control	Matching (Simple)	Australia	7

Egorova et al (2015)[56]	Retrospective cohort	Matching (Simple)	USA	5
Flagg et al (2014)[57]	Retrospective cohort	Matching (Simple)	USA	5
Keshavamurthy et al (2014)[60]	Prospective cohort	Matching (Simple)	USA	7
Pakyz et al (2011)[63]	Retrospective case-control	Matching (Simple)	USA	4
Chen et al (2017)[54]	Retrospective cohort	Regression	Australia	6
Eckmann et al (2013)[55]	Retrospective cohort	Regression	UK	7
Lipp et al (2012)[61]	Retrospective cohort	Regression	USA	5
Yasunaga et al (2012)[70]	Retrospective cohort	Regression	Japan	5
Zerey et al (2007)[71]	Retrospective cohort	Regression	USA	5
Jacob et al (2017)[59]	Retrospective cohort	Matching (Time)	USA	8
Ryan et al (2017)[64]	Retrospective cohort	Matching (Time)	Ireland	7
Tabak et al (2013)[67]	Retrospective cohort	Matching (Time)	USA	8
Vonberg et al (2008)[69]	Prospective case-control	Matching (Time)	Germany	7
Vrijens et al (2012)[50]	Retrospective cohort	Matching (Time)	Belgium	8
Foster et al (2012)[58]	Retrospective cohort	Survival Analysis	Canada	8
Mitchell et al (2014)[62]	Retrospective cohort	Multistate Modelling	Australia	6
Stevens et al (2015)[66]	Retrospective cohort	Multistate Modelling	USA	8
van Kleef et al (2014)[68]	Prospective cohort	Multistate Modelling	UK	8
Surgical Site Infection				
Kuy et al (2014)[88]	Retrospective cohort	Group comparison	USA	5
Lamarsalle et al (2013)[89]	Retrospective cohort	Group comparison	France	4
Anderson et al (2009)[73]	Prospective case-control	Matching (Simple)	USA	7
Apisarnthanarak et al (2003)[74]	Prospective case-control	Matching (Simple)	USA	7
Atkinson et al (2017)[76]	Prospective cohort	Matching (Simple)	UK	6
Coskun et al (2005)[78]	Prospective cohort	Matching (Simple)	Turkey	6
Delgado-Rodriguez et al (1997)[80]	Prospective cohort	Matching (Simple)	Spain	7
Gaine et al (2000)[82]	Prospective case-control	Matching (Simple)	UK	6
Gonzalez-Velez et al (2016)[84]	Prospective case-control	Matching (Simple)	Spain	7
Jenks et al (2014)[86]	Retrospective cohort	Matching (Simple)	UK	7
Kusachi et al (2012)[87]	Prospective case-control	Matching (Simple)	Japan	7
Merle et al (2000)[91]	Prospective cohort	Matching (Simple)	France	7
Monge Jodra et al (2006)[92]	Prospective case-control	Matching (Simple)	Spain	7
Olsen et al (2010)[93]	Retrospective cohort	Matching (Simple)	USA	5
Peng et al (2006)[42]	Retrospective cohort	Matching (Simple)	USA	7
Pollard et al (2006)[94]	Retrospective cohort	Matching (Simple)	UK	5

Asensio and Torres (1999)[75]	Retrospective cohort	Regression	Spain	7
Boltz et al (2011)[77]	Prospective cohort	Regression	USA	7
Fukuda et al (2012)[81]	Retrospective cohort	Regression	Japan	7
Geubbels et al (2000)[83]	Prospective cohort	Regression	Netherlands	6
McGarry et al (2004)[90]	Prospective cohort	Regression	USA	7
Plowman et al (2001)[43]	Prospective cohort	Regression	UK	7
Roberts et al (2010)[47]	Retrospective cohort	Regression	USA	7
Glied et al (2016)[37]	Retrospective cohort	Matching (Time)	USA	8
Vrijens et al (2012)[50]	Retrospective cohort	Matching (Time)	Belgium	8
Herwaldt et al (2006)[85]	Prospective cohort	Survival Analysis	USA	8
De Angelis et al (2011)[79]	Prospective cohort	Multistate Modelling	Switzerland	8
Healthcare Associated Infection				
Dulworth and Pyenson (2004)[97]	Retrospective cohort	Group comparison	USA	4
Grandini and Caramelli (2006)[98]	Retrospective cohort	Group comparison	Brazil	6
Kollef et al (1997)[104]	Prospective cohort	Group comparison	USA	5
Nosrati et al (2010)[108]	Prospective cohort	Group comparison	Iran	6
Chacko et al (2017)[96]	Prospective cohort	Group comparison	India	4
O'Keefe et al (2017)[109]	Retrospective cohort	Group comparison	Canada	5
Delgado-Rodriguez et al (1997)[80]	Prospective cohort	Matching (Simple)	Spain	7
Khan and Celik (2001)[103]	Prospective cohort	Matching (Simple)	Turkey	6
Resch et al (2009)[110]	Retrospective cohort	Matching (Simple)	Germany	5
Karagozian et al (2010)[102]	Retrospective cohort	Matching (Simple)	USA	7
Wu et al (2008)[112]	Retrospective cohort	Matching (Simple)	USA	5
Campbell et al (2015)[95]	Retrospective cohort	Regression	USA	6
Graves et al (2007)[99]	Prospective cohort	Regression	Australia	7
Hassan et al (2010)[100]	Retrospective cohort	Regression	USA	5
Hoogervorst-Schilp et al (2015)[101]	Retrospective cohort	Regression	Netherlands	6
Lee et al (2011)[105]	Retrospective cohort	Regression	Japan	5
Lloyd-Smith et al (2013)[106]	Retrospective case-control	Regression	Canada	5
Plowman et al (2001)[43]	Prospective cohort	Regression	UK	6
Roberts et al (2010)[47]	Retrospective cohort	Regression	USA	7
Trybou et al (2013)[111]	Retrospective cohort	Regression	Belgium	7
Nelson et al (2015)[113]	Retrospective cohort	Matching (Time)	USA	8
Vrijens et al (2012)[50]	Retrospective cohort	Matching (Time)	Belgium	8
Herwaldt et al (2006)[85]	Prospective cohort	Survival Analysis	USA	8

Arefian et al (2016)[4]	Prospective cohort	Multistate Modelling	Germany	7
De Angelis et al (2011)[79]	Prospective cohort	Multistate Modelling	Switzerland	8
Macedo-Viñas et al (2013)[107]	Retrospective cohort	Multistate Modelling	Switzerland	7
Urinary Tract Infection				
Delgado-Rodriguez et al (1997)[80]	Prospective cohort	Matching (Simple)	Spain	7
Peng et al (2006)[42]	Retrospective cohort	Matching (Simple)	USA	7
Dasenbrock et al (2016)[35]	Retrospective cohort	Regression	USA	5
Ingeman et al (2011)[114]	Retrospective cohort	Regression	Denmark	5
Nosova et al (2013)[115]	Retrospective cohort	Regression	USA	5
Plowman et al (2001)[43]	Prospective cohort	Regression	UK	7
Rattanaumpawan et al (2017)[45]	Retrospective cohort	Regression	Thailand	7
Roberts et al (2010)[47]	Retrospective cohort	Regression	USA	7
Glied et al (2016)[37]	Retrospective cohort	Matching (Time)	USA	8
Vrijens et al (2012)[50]	Retrospective cohort	Matching (Time)	Belgium	8
Pneumonia				
Zhang and Duan (2015)[118]	Prospective cohort	Group comparison	China	4
Micek et al (2016)[116]	Retrospective case-control	Matching (Simple)	USA	6
Peng et al (2006)[42]	Retrospective cohort	Matching (Simple)	USA	7
Restrepo et al (2010)[117]	Retrospective cohort	Matching (Simple)	USA	6
Dasenbrock et al (2016)[35]	Retrospective cohort	Regression	USA	5
Ingeman et al (2011)[114]	Retrospective cohort	Regression	Denmark	5
Roberts et al (2010)[47]	Retrospective cohort	Regression	USA	7
Glied et al (2016)[37]	Retrospective cohort	Matching (Time)	USA	8
Lower Respiratory Tract Infection (other than pneumonia)				
Delgado-Rodriguez et al (1997)[80]	Prospective cohort	Matching (Simple)	Spain	7
Graves et al (2007)[99]	Prospective cohort	Regression	Australia	7
Plowman et al (2001)[43]	Prospective cohort	Regression	UK	7
Vrijens et al (2012)[50]	Retrospective cohort	Matching (Time)	Belgium	8
Bone and Joint Infection				
Padegimas et al (2015)[119]	Retrospective cohort	Group comparison	USA	4

Supplementary Material 2

The PubMed search strategy is presented in three parts. The first part has cross-infection keywords and Mesh terms. The second part has HAI related keywords and Mesh terms. The third part has economic and length of stay keywords and Mesh terms.

Cross Infection

((“Cross Infection”[Mesh] OR (cross infection*[tiab]) OR (healthcare associated infection*[tiab]) OR (health care associated infection*[tiab]) OR (hospital acquired infection*[tiab]) OR (hospital-acquired infection*[tiab]) OR (hospital associated infection*[tiab]) OR (healthcare-associated infection*[tiab]) OR (healthcare acquired infection*[tiab]) OR (health care acquired infection*[tiab]) OR (nosocomia*[tiab]) OR “Disease Transmission, Infectious”[Mesh] OR (cross transmission[tiab]) OR (infectious disease transmission[tiab]))

Healthcare Associated Infections

(“Catheter-Related Infections”[Mesh] OR (catheter related infection*[tiab]) OR (catheter acquired infection*[tiab]) OR (catheter associated infection*[tiab]) OR (CAUTI[tiab]) OR (device related infection*[tiab]) OR (device acquired infection*[tiab]) OR (device associated infection*[tiab]) OR (central line related bloodstream infection*[tiab]) OR (central line acquired bloodstream infection*[tiab]) OR (central line associated bloodstream infection*[tiab]) OR (CLABSI[tiab]) OR(CRBSI[tiab]) OR “bacteremia”[Mesh] OR (bacteremia[tiab]) OR “Methicillin-Resistant Staphylococcus aureus”[Mesh] OR "Clostridium difficile"[Mesh] OR "Clostridium Infections"[Mesh] OR "Enterocolitis, Pseudomembranous"[Mesh] OR (Clostridium difficile[tiab]) OR (c. diff*[tiab]) OR (CDI[tiab]) OR (CDAD[tiab]) OR (gastrointestinal infection*[tiab]) OR “norovirus”[Mesh] OR "Pneumonia, Ventilator-Associated"[Mesh] OR “Respiratory Tract Infections”[Mesh] OR (ventilator acquired pneumonia[tiab]) OR (nosocomial pneumonia[tiab]) OR (ventilator associated pneumonia[tiab]) OR “sepsis”[Mesh] OR "Urinary Tract Infections"[Mesh] OR "Urinary Catheterization"[Mesh] OR (urinary catheter*[tiab]) OR "Surgical Wound Infection"[Mesh] OR (surgical site infection*[tiab]) OR (postoperative infection*[tiab]) OR (postsurgical infection*[tiab]) OR (wound infection*[tiab]) OR (sternal wound infection*[tiab]) OR (postoperative[tiab]) OR (post-surgical[tiab]) OR “Cardiovascular Infections”[Mesh] OR “endocarditis, bacterial”[Mesh] OR (cardiovascular infection*[tiab]) OR (endocarditis[tiab]) OR (pericarditis[tiab]) OR “Staphylococcal Skin Infections”[Mesh] OR (skin infection*[tiab]) OR (soft tissue infection*[tiab]) OR “Osteomyelitis”[Mesh] OR (bone infection*[tiab]) OR (joint infection*[tiab]) OR “central nervous system infections”[Mesh] OR “eye infections”[Mesh] OR (eye infection*[tiab]) OR “otitis”[Mesh] OR ear infection*[tiab] OR “Sinusitis”[Mesh] OR (mouth infection*[tiab]) OR “reproductive tract infections”[Mesh] OR (reproductive tract infection*[tiab]))))

Economics and length of stay

("Costs and Cost Analysis"[Mesh] OR "Health Care Costs"[Mesh] OR "Health Expenditures"[Mesh] OR "Direct Service Costs"[Mesh] OR "Hospital Costs"[Mesh] OR "Employer Health Costs"[Mesh] OR "Drug Costs"[Mesh] OR "Cost of Illness"[Mesh] OR "Economics"[Mesh] OR "Length of Stay"[Mesh] OR (length of stay[tiab]) OR (length of hospitalization[tiab]) OR (hospitalization length[tiab]) OR (duration of stay[tiab]))

Supplementary Material 3

Newcastle-Ottawa quality assessment tool

This scale has been adapted from the Newcastle-Ottawa Quality Assessment Scale to perform quality assessment (QA) in the systematic review. In this version of NOS we define the exposure as HAI and the outcome as discharge or total duration of hospital stay.

COHORT STUDIES

Selection: (Maximum 5 stars)

1) Representativeness of the sample:

a) Truly representative of the average in the target population (e.g. inpatient hospital specialty)**

b) Somewhat representative of the average in the target population*

c) Selected group of users.

d) No description of the sampling strategy.

2) Sample size:

a) Adequate sample size to be able to draw conclusions about impact*

b) Very small sample size.

3) Ascertainment of the exposure:

a) Case definitions applied to records (eg electronic medical records, microbiology results)**
b) Nurses, doctors or laboratory tests only to identifying exposure*
c) Exposure assumed retrospectively purely due to treatment (i.e. antibiotics) or with ICD codes
d) written, self-reported or self-assessed
e) no description

continues next page

Comparability: (Maximum 1 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.

a) The study controls for additional factors (such as age, comorbidities, device use/not an exhaustive list of factors)*

b) The study does not control for additional factors.

Outcome: (Maximum 2 stars)

1) Assessment of the outcome:

a) Clearly reported total duration of hospitalisation*

b) Duration of hospitalisation is reported but unclear if it refers to total.

2) HAI treated as a time-dependent exposure:

a) The statistical methods used to analyse the data control for bias that can occur if baseline immeasurable time-dependent factors that cannot be recorded at baseline and change value after patient observation starts are analysed as if they were known and available at baseline.*

b) The statistical methods do not treat HAI as a time-dependent exposure.

For case-control studies use items on next page

CASE-CONTROL STUDIES

Adapted from the Newcastle-Ottawa Quality Assessment Scale. Cases refer to HAI patients and control patients refer to non-HAI patients.

Selection: (Maximum 5 stars)

1) Is the case definition adequate?
   a) Case definitions applied to records (eg electronic medical records, microbiology results)**
   b) Nurses, doctors or laboratory tests only to identifying exposure*
   c) Exposure assumed retrospectively purely due to treatment (i.e. antibiotics) or with ICD codes
   d) written, self-reported or self-assessed
   e) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases*
   b) potential for selection biases or not stated

3) Selection of Controls
   a) controls from same target population chosen prospectively**
   b) controls from diverse population chosen retrospectively*
   c) no description

Comparability (Maximum 1 stars)

1) Comparability of cases and controls on the basis of the design or analysis
   a) The study controls for additional factors.*
   b) The study does not control for additional factors.

Outcome (Maximum 2 stars)

1) Assessment of the outcome:

   a) Clearly reported total duration of hospitalisation*

   b) Duration of hospitalisation is reported but unclear if it refers to total.

2) HAI treated as a time-dependent exposure:

   a) The statistical methods used to analyse the data control for bias that can occur if baseline immeasurable time-dependent factors that cannot be recorded at baseline and change value after patient observation starts are analysed as if they were known and available at baseline.*

   b) The statistical methods do not treat HAI as a time-dependent exposure.

Supplementary Material 4

Table shows quality assessment breakdown for each study. Quality assessment was performed with the Newcastle-Ottawa Scale (NOS). Headings on table are named after items in the cohort/case control versions of NOS where applicable. Each study could be awarded a maximum of 8 stars.

Authors	Sample representative/Case definitions adequate	Sample size/Representativeness of cases	Ascertainment of exposure/Selection controls	Study controls for additional factors	Assessment of outcome	HAI treated as a time varying exposure	Total
Bloodstream Infection							
Riu et al (2016)[46]	2	1	2	0	1	0	6
Al-Rawajfah et al (2012)[31]	0	1	1	1	1	0	4
Caballero-Granado et al (2001)[34]	2	1	2	0	1	0	6
Kothari et al (2009)[40]	2	1	2	1	1	0	7
Molina et al (2013)[41]	2	1	2	1	1	0	7
Peng et al (2006)[42]	2	1	2	1	1	0	7
Primo et al (2012)[44]	2	1	1	0	1	0	5
Song et al (2003)[48]	2	1	2	0	1	0	6
Butler et al (2010)[33]	2	1	1	1	1	0	6
Dasenbrock et al (2016)[35]	2	1	0	1	1	0	5
Plowman et al (2001)[43]	2	0	2	1	1	0	6
Rattanaumpawan et al (2017)[45]	2	1	2	1	1	0	7
Roberts et al (2010)[47]	2	1	2	1	1	0	7
Al-Rawajfah et al (2013)[30]	2	1	1	1	1	1	7

de Kraker et al (2011)[36]	2	1	1	1	1	1	7
Glied et al (2016)[37]	2	1	2	1	1	1	8
Grupper et al (2007)[38]	2	0	1	1	1	1	6
Kaye et al (2014)[39]	2	1	2	1	1	1	8
Vrijens et al (2010)[51]	2	1	2	1	1	1	8
Vrijens et al (2012)[50]	2	1	2	1	1	1	8
Barnett et al (2013)[32]	2	1	1	1	1	1	7
Stewardson et al (2013)[49]	2	1	2	1	1	1	8
Stewardson et al (2016)[26]	2	1	1	1	1	1	7
Gastrointestinal Infection							
Abdelsattar et al (2015)[52]	2	1	1	0	1	0	5
Skovrlj et al (2014)[65]	2	1	0	0	0	0	3
Zhang et al (2016)[72]	2	1	1	0	1	0	5
Bond et al (2017)[53]	2	1	2	1	1	0	7
Egorova et al (2015)[56]	2	1	0	1	1	0	5
Flagg et al (2014)[57]	2	1	0	1	1	0	5
Keshavamurthy et al (2014)[60]	2	1	2	1	1	0	7
Pakyz et al (2011)[63]	0	1	1	1	1	0	4
Chen et al (2017)[54]	2	1	1	1	1	0	6
Eckmann et al (2013)[55]	2	1	2	1	1	0	7
Lipp et al (2012)[61]	2	1	0	1	1	0	5
Yasunaga et al (2012)[70]	2	1	0	1	1	0	5

Zerey et al (2007)[71]	2	1	0	1	1	0	5
Jacob et al (2017)[59]	2	1	2	1	1	1	8
Ryan et al (2017)[64]	2	1	1	1	1	1	7
Tabak et al (2013)[67]	2	1	2	1	1	1	8
Vonberg et al (2008)[69]	1	1	2	1	1	1	7
Vrijens et al (2012)[50]	2	1	2	1	1	1	8
Foster et al (2012)[58]	2	1	2	1	1	1	8
Mitchell et al (2014)[62]	2	1	1	0	1	1	6
Stevens et al (2015)[66]	2	1	2	1	1	1	8
van Kleef et al (2014)[68]	2	1	2	1	1	1	8
Surgical Site Infection							
Kuy et al (2014)[88]	2	0	2	0	1	0	5
Lamarsalle et al (2013)[89]	2	1	0	0	1	0	4
Anderson et al (2009)[73]	2	1	2	1	1	0	7
Apisarnthanarak et al (2003)[74]	2	1	2	1	1	0	7
Atkinson et al (2017)[76]	2	0	2	1	1	0	6
Coskun et al (2005)[78]	2	0	2	1	1	0	6
Delgado-Rodriguez et al (1997)[80]	2	1	2	1	1	0	7
Gaine et al (2000)[82]	1	1	2	1	1	0	6
Gonzalez-Velez et al (2016)[84]	2	1	2	1	1	0	7
Jenks et al (2014)[86]	2	1	2	1	1	0	7
Kusachi et al (2012)[87]	2	1	2	1	1	0	7

Merle et al (2000)[91]	2	1	2	1	1	0	7
Monge Jodra et al (2006)[92]	2	1	2	1	1	0	7
Olsen et al (2010)[93]	2	1	0	1	1	0	5
Peng et al (2006)[42]	2	1	2	1	1	0	7
Pollard et al (2006)[94]	2	0	1	1	1	0	5
Asensio and Torres (1999)[75]	2	1	2	1	1	0	7
Boltz et al (2011)[77]	2	1	2	1	1	0	7
Fukuda et al (2012)[81]	2	1	2	1	1	0	7
Geubbels et al (2000)[83]	2	1	1	1	1	0	6
McGarry et al (2004)[90]	2	1	2	1	1	0	7
Plowman et al (2001)[43]	2	1	2	1	1	0	7
Roberts et al (2010)[47]	2	1	2	1	1	0	7
Glied et al (2016)[37]	2	1	2	1	1	1	8
Vrijens et al (2012)[50]	2	1	2	1	1	1	8
Herwaldt et al (2006)[85]	2	1	2	1	1	1	8
De Angelis et al (2011)[79]	2	1	2	1	1	1	8
Healthcare Associated Infection							
Dulworth and Pyenson (2004)[97]	2	1	0	0	1	0	4
Grandini and Caramelli (2006)[98]	2	1	2	0	1	0	6
Kollef et al (1997)[104]	2	0	2	0	1	0	5
Nosrati et al (2010)[108]	2	1	2	0	1	0	6
Chacko et al (2017)[96]	2	0	1	0	1	0	4

O'Keefe et al (2017)[109]	2	1	1	0	1	0	5
Delgado-Rodriguez et al (1997)[80]	2	1	2	1	1	0	7
Khan and Celik (2001)[103]	2	1	1	1	1	0	6
Resch et al (2009)[110]	2	1	0	1	1	0	5
Karagozian et al (2010)[102]	2	1	2	1	1	0	7
Wu et al (2008)[112]	2	1	0	1	1	0	5
Campbell et al (2015)[95]	2	1	1	1	1	0	6
Graves et al (2007)[99]	2	1	2	1	1	0	7
Hassan et al (2010)[100]	2	1	0	1	1	0	5
Hoogervorst-Schilp et al (2015)[101]	2	1	1	1	1	0	6
Lee et al (2011)[105]	2	1	0	1	1	0	5
Lloyd-Smith et al (2013)[106]	1	1	1	1	1	0	5
Plowman et al (2001)[43]	2	1	1	1	1	0	6
Roberts et al (2010)[47]	2	1	2	1	1	0	7
Trybou et al (2013)[111]	2	1	2	1	1	0	7
Nelson et al (2015)[113]	2	1	2	1	1	1	8
Vrijens et al (2012)[50]	2	1	2	1	1	1	8
Herwaldt et al (2006)[85]	2	1	2	1	1	1	8
Arefian et al (2016)[4]	2	1	2	0	1	1	7
De Angelis et al (2011)[79]	2	1	2	1	1	1	8
Macedo-Viñas et al (2013)[107]	2	1	1	1	1	1	7
Urinary Tract Infection							

Delgado-Rodriguez et al (1997)[80]	2	1	2	1	1	0	7
Peng et al (2006)[42]	2	1	2	1	1	0	7
Dasenbrock et al (2016)[35]	2	1	0	1	1	0	5
Ingeman et al (2011)[114]	2	1	0	1	1	0	5
Nosova et al (2013)[115]	2	1	0	1	1	0	5
Plowman et al (2001)[43]	2	1	2	1	1	0	7
Rattanaumpawan et al (2017)[45]	2	1	2	1	1	0	7
Roberts et al (2010)[47]	2	1	2	1	1	0	7
Glied et al (2016)[37]	2	1	2	1	1	1	8
Vrijens et al (2012)[50]	2	1	2	1	1	1	8
Pneumonia							
Zhang and Duan (2015)[118]	2	0	1	0	1	0	4
Micek et al (2016)[116]	2	1	1	1	1	0	6
Peng et al (2006)[42]	2	1	2	1	1	0	7
Restrepo et al (2010)[117]	2	1	1	1	1	0	6
Dasenbrock et al (2016)[35]	2	1	0	1	1	0	5
Ingeman et al (2011)[114]	2	1	0	1	1	0	5
Roberts et al (2010)[47]	2	1	2	1	1	0	7
Glied et al (2016)[37]	2	1	2	1	1	1	8
Lower Respiratory Tract Other Infection							
Delgado-Rodriguez et al (1997)[80]	2	1	2	1	1	0	7
Graves et al (2007)[99]	2	1	2	1	1	0	7

Plowman et al (2001)[43]	2	1	2	1	1	0	7
Vrijens et al (2012)[50]	2	1	2	1	1	1	8
Bone and Joint Infection							
Padegimas et al (2015)[119]	2	1	0	0	1	0	4

Supplementary Material 5

Details of Statistical Methods in the Systematic Review

Statistical Method	Description	Advantages	Disadvantages	Studies
Group Comparison	Naive comparison of means between an infected and an uninfected group. Simple method of analysis that takes advantage of raw data. The groups may not be similar due to differing characteristics (e.g. age, comorbidities) of patients in the HAI group.	Easy to use and only requires very basic data such as the presence of HAI or not which is possible from routine data and may not require data collection.	Leads to biased estimates because patients in the infected group tend to be sicker and ignores time-exposure. Suffers from selection and time-dependent bias.	[46, 52, 65, 72, 88, 89, 96-98, 104, 108, 109, 118, 119]
Matching (Simple)	Matching methods are very popular and include one to one or to more than one matching and matching using propensity scores. Usually matching methods compare mean LOS between the two matched groups and "simple" here denotes matching on any characteristic other than the time a patient has stayed in hospital up to the point of infection (time to infection).	Easy to use and there are many techniques available to match cases to controls. Usual matching factors include: Age, sex, comorbidities and ward or admission type. It is possible to use other statistical techniques on a matched sample.	Simple matching when estimating the extra LOS due to infection gives biased estimates due to time-dependent bias. This bias occurs because the time before infection is used when estimating the extra LOS. There is also a trade-off between accuracy and maximising successful matches.	[31, 34, 40-42, 44, 48, 53, 56, 57, 60, 63, 73, 74, 76, 78, 80, 82, 84, 86, 87, 91-94, 102, 103, 110, 112, 116, 117]
Regression	These methods estimate LOS attributable to HAI by controlling for a range of patient characteristics and comorbidities using linear regression	Fairly straightforward methods that can be used to estimate the impact of HAI on LOS. Ease of estimation and interpretation. Ease of controlling for comorbidities.	Regression methods do not control for the timing of events so they suffer from time-dependent bias.	[33, 35, 43, 45, 47, 54, 55, 61, 70, 71, 75, 77, 81, 83, 90, 95, 99-101, 105, 106, 111, 114, 115]
Matching (Time)	Methods that primarily match on the time to infection for controlling time-dependent HAI exposure. Controls are required to have spent as much time in hospital as the case at the time of infection. Other matching factors include age, sex, comorbidities.	In addition to usual factors matching can include exposure time. Matching using incidence density sampling, which also matches on time to infection, has been suggested as the best way to mitigate time-dependent bias.	Simply adding time to infection as a matching factor will not completely eliminate time-dependent bias. Incidence density matching performs better but it is a complicated procedure which is second best to truly time-varying methods such as multistate modelling.	[30, 36-39, 50, 51, 59, 64, 67, 69, 113]
Survival Analysis	Cox survival models treating HAI as time-fixed covariate but can be adapted to control for time-dependent bias.	Survival methods can be adapted for time-dependent analysis using Cox models producing unbiased estimates. Can adjust for comorbidities.	Survival methods require more in depth statistical knowledge and data manipulation to control for time dependence. Proportional hazards models use strong assumptions that are not always realistic.	[58, 85]
Multistate Modelling	Patient data are modelled between a set of states over time such as HAI and discharge. A survival analysis is then run for every transition (a change from one state to the other such as hospital to HAI or discharged).	This method treats HAI as a time-dependent exposure therefore properly controlling for the occurrence of events over the course of time. Competing-risks can be analysed at the same time. Basic multistate analysis can be performed with a pocket calculator.	Multistate modelling can be complicated and requires data preparation and specialised software to be able to control for other important covariates such as comorbidities. Even then controlling for characteristics can only be done indirectly.	[4, 26, 32, 49, 62, 66, 68, 79, 107]

Author contributions

SM: Led on manuscript development, design of literature search, data extraction, data analysis, statistical analysis and quality assessment.

SS: Contributed on manuscript development, design of literature search, data extraction, data analysis, and quality assessment.

SD: Read, edited and commented on initial analysis; shaped, commented and revised subsequent drafts.

NG: Read, edited and commented on initial analysis; shaped, commented and revised subsequent drafts.

HM: Contributed on manuscript development and shaped commented and revised subsequent drafts.

AM: Contributed on data extraction, quality assessment and commented and revised subsequent drafts.

CR: Contributed on statistical analysis and revised commented and revised subsequent drafts.

JR: Contributed on design of literature search and commented and revised subsequent drafts.